

The role of factors associated with the course of pregnancy and childbirth in attention deficit hyperactivity disorder (ADHD)

Elżbieta Lipińska¹, Agnieszka Słopeń², Natalia Pytlińska²,
Radosław Słopeń³, Tomasz Wolańczyk¹, Anita Bryńska¹

¹ Medical University of Warsaw, Department of Child and Adolescent Psychiatry

² Poznan University of Medical Sciences, Department of Child and Adolescent Psychiatry

³ Poznan University of Medical Sciences, Department of Gynecological Endocrinology

Summary

Aim. Assessment of the prevalence of risk factors associated with the course of pregnancy and childbirth and the condition of the child after birth in a group of children and adolescents with ADHD and a control group.

Material. 205 unrelated children and adolescents diagnosed with ADHD and 106 primary and secondary school students aged 7–17.

Method. Mothers of children and adolescents diagnosed with ADHD, and those from the control group, were asked to provide a medical history in order to obtain data to supplement the *Pregnancy and perinatal history questionnaire*.

Results. Statistically significant differences ($p < 0.05$) were demonstrated for the incidence rates of factors related to the course of pregnancy and childbirth such as: the occurrence of maternal diseases during pregnancy, especially in the I/II trimester, and other problems during pregnancy; exposure to stress and taking medication during pregnancy; smoking during pregnancy; mother's age at childbirth, i.e., < 25 years or > 35 years; use of pain reducing substances during labor and problems with the child during the delivery; an APGAR score in the range of 5–7 points; the occurrence of neonatal jaundice necessitating treatment, especially replacement transfusion; physical anomalies or other congenital problems in the newborn, as well as adaptive problems necessitating neonatal oxygen administration or placement in an incubator.

Conclusions. Significantly more frequent occurrence of risk factors related to the course of pregnancy, childbirth and the child's condition after birth in the ADHD group may indicate their potential role in the etiology of ADHD.

Key words: attention deficit hyperactivity disorder, etiology, environmental factors

Introduction

Attention deficit hyperactivity disorder (ADHD) occurs worldwide, in all cultures. Its worldwide prevalence is estimated at an average of about 5.3% in the population of children and adolescents, and its etiology is multifactorial. About 80% of ADHD causes have a genetic basis [1, 2], the remaining 20% are related to the influence of environmental factors [2, 3]. In the context of observations on the significance of the environmental impact on genetic material (Gene-Environment Interactions – GxE), and thus the expression of genes and the final clinical picture of disorders, the environmental factors, especially those related to the course of pregnancy and childbirth, become particularly important [4]. Study results indicate a greater risk of the symptoms of the disorder as a consequence of prenatal factors such as: cigarette smoking during pregnancy [5–9], alcohol consumption during pregnancy [10, 11], combined effects of nicotine and alcohol [12], poor quality of life of the pregnant woman associated primarily with the experience of excessive stress during pregnancy, the occurrence of depression in the pregnant woman [4, 7, 13], low socio-economic status, and the mother's lack of education [10]. Research also shows a relationship between attention deficit hyperactivity disorder and parameters describing the condition of the newborn, such as: low birth weight [14, 15], prematurity [16], low APGAR score [17–19], high hyperbilirubinemia [20, 21]. The above observations justify continuing research into the role of environmental factors in the etiology of ADHD.

Aim

The aim of the study was an assessment of the prevalence of risk factors associated with the course of pregnancy and childbirth and the condition of the child after birth, in a group of children and adolescents with ADHD and a control group, and intergroup comparisons.

Material

205 unrelated children and adolescents aged 7–17 (mean age 10.8, $SD = 2.7$), including 187 boys (91%) and 18 girls (9%), diagnosed with attention deficit hyperactivity disorder took part in the study, all of whom were patients at the psychiatric ward or the outpatient psychiatric clinic (the ADHD group). Diagnosis of attention deficit hyperactivity disorder was based on DSM-IV-TR [22] and ICD-10 [23] diagnostic criteria. In the test group, patients with combined type ADHD according to DSM were the most numerous ($n = 147$; 71.7%), followed by predominantly inattentive type ADHD ($n = 45$; 22%). Additionally, 6.3% ($n = 13$) of the test subjects were diagnosed with predominantly hyperactive-impulsive type ADHD. Exclusion criteria from the test group were: diagnosis of schizophrenia, bipolar disorder, overall developmental disorders or somatic disorders, and lack of consent for participation in the study.

The control group consisted of 106 healthy primary and secondary school students from Warsaw and the surrounding area, aged 7–17 (mean age 10.6, $SD = 2.7$), including 64 boys (60%) and 42 girls (40%) (selection based on age and gender criterion), who have never used psychological, psychiatric or psychotherapeutic services, and who were unrelated to the patients (the above information was obtained on the basis of a medical history collected by the doctor conducting the study).

Method

Research tools

Structured history questionnaire towards attention deficit hyperactivity disorder according to ICD-10 and DSM-IV [24] – a structured medical history interview, consisting of 18 questions regarding the presence and severity of individual symptoms of attention deficit hyperactivity disorder, and questions about the child’s functioning and the presence of other mental disorders. It allows to determine the diagnosis and define the type of the disorder (predominantly inattentive type, predominantly hyperactive-impulsive type, combined type). The severity of symptoms is assessed on a four-level scale from 0 to 3. Answers “no” (0) and “probably no” (1) are coded as no symptoms, answers “mostly yes” (2) and “yes” (3) are coded as the presence of a symptom.

Pregnancy and perinatal history questionnaire – consists of about 40 questions regarding the course of the pregnancy, the perinatal period, and early child development (modification of the questionnaire by Buka et al., 2000 [25]). It contains detailed questions about: (1) maternal diseases before conception; (2) course of the pregnancy: maternal diseases during pregnancy, nausea and vomiting, mother’s weight, hypertension, seizures, falls and injuries, amount of amniotic fluid, spotting and bleeding, risk of premature delivery, premature rupture of the amniotic sac, serological conflict, exposure to stress, medication intake, smoking, alcohol consumption, use of drugs and medication of unknown origin; (3) factors related to the course of delivery: maternal age at the time of delivery, single/multiple delivery, delivery date, type of delivery, use of induction drugs, use of labor pain reducing substances, child position during delivery, changes in the amniotic fluid, problems with the placenta, bleeding during delivery, problems with the child during delivery, wrapping of umbilical cord around the child’s neck; (4) factors related to the condition of the child after birth: body weight, APGAR score, neonatal oxygen administration, indications for and placement in an incubator, neonatal jaundice and type of treatment, physical anomalies and other congenital problems.

Research procedure

In order to verify the diagnosis in the ADHD group, *the structured history questionnaire towards attention deficit hyperactivity disorder according to ICD-10 and DSM-IV* was conducted. Next, mothers of the patients diagnosed with ADHD and those

from the control group were asked for a medical history (also based on data from the Child's Health Book) in order to obtain data needed to complete *the Pregnancy and perinatal history questionnaire*. The study was approved by the Bioethics Commission at the Medical University of Warsaw (MUW).

Statistical analysis

The Kolmogorov-Smirnov test was used to check the normality of variable distributions. Descriptive statistics were used: numerical and percentage frequencies, means, standard deviations. The chi-squared test was used to compare the distribution of results. The significance of differences between means was analyzed using student's t-test or one-way analysis of variance, and in the absence of normal distribution the Mann-Whitney test was used. The significance level was $p < 0.05$. The analyses were carried out using the SPSS statistics package.

Results

The analyses did not take into account "I don't know" answers. Information on individual variables were not always obtained from all respondents, hence the analyses of factor significance were carried out for groups of varying sizes.

Factors associated with the course of pregnancy

Statistically significant differences between ADHD and control groups were found with respect to eight variables. The occurrence of maternal diseases during pregnancy was confirmed in 34.7% of the responders from the ADHD group and 14.4% from the control group ($p = 0.0001$). In the ADHD group, maternal diseases occurred most frequently in the I/II trimester (56.4%), in almost one third of respondents (30.9%) they lasted throughout the entire pregnancy. The group of women who were ill during the III trimester was the least numerous (12.7%). In turn, in the control group, the majority of women declared health problems throughout their entire pregnancy (66.7%), and every third mother (33.3%) reported that she was ill in the III trimester of pregnancy. Other problems during pregnancy (not mentioned in the questionnaire) concerned 14.5% of mothers in the ADHD group and 3.8% of women in the control group ($p = 0.005$).

Exposure to stress or emotional problems during pregnancy were confirmed by 53.8% of mothers in the ADHD group, most often during the entire pregnancy (57.3%), more than a third (36.0%) experienced them during the I/II trimester, and 6.7% during the III trimester. In the control group, exposure to stress or emotional problems during pregnancy affected 27.6% of women, of which 42.9% declared such problems in the III trimester of pregnancy, 28.6% in the I/II trimester or throughout the entire pregnancy. Over 40% of mothers in the ADHD group (43.5%) used medication during pregnancy,

and the number of women in the control group who declared taking medication during pregnancy was 31.4% ($p = 0.047$). In the ADHD group, the use of medication most often took place during the entire pregnancy (49.3%), in more than a third of women (36.2%) during the I/II trimester, and in the case of 14.5% during the III trimester (no analysis of the type of medication was conducted). In the control group, the majority of women declared taking medication during pregnancy in the III trimester (46.9%). 31.3% of mothers reported that this took place in the I/II trimester, and in the case of 21.9% medication use took place during the entire pregnancy.

Most of the women in both groups did not smoke during pregnancy. Nevertheless, more than one-fourth of mothers from the ADHD group (27.3%) and 8.5% of mothers from the control group admitted to such behavior ($p = 0.0001$). In the ADHD group, smoking during pregnancy most frequently concerned the entire pregnancy (72.9%), in the case of 25.0% – the I/II trimester, and in the case of 2.1% – only the III trimester. Similarly, in the control group, the majority of women declared smoking during pregnancy throughout its duration (88.9%), and in the case of 11.1% it was in the I/II trimester. Detailed data are presented in Table 1.

Table 1. Incidence of risk factors associated with pregnancy in the ADHD and control groups (variables for which statistically significant differences were demonstrated)

Factor	Answer	ADHD group n (%)	Control group n (%)	p
Maternal diseases during pregnancy	yes	61 (34.7)	15 (14.4)	0.0001
	no	115 (65.3)	89 (85.6)	
Period during which maternal diseases occurred in pregnancy	I/II trimester	31 (56.4)	0 (0.0)	0.0001
	III trimester	7 (12.7)	5 (33.3)	
	entire pregnancy	17 (30.9)	10 (66.7)	
Other problems during pregnancy	yes	24 (14.5)	4 (3.8)	0.005
	no	142 (85.5)	101 (96.2)	
Stress or emotional problems during pregnancy	yes	91 (53.8)	29 (27.6)	0.0001
	no	78 (46.2)	76 (72.4)	
Period during which stress and emotional problems occurred in pregnancy	I/II trimester	32 (36.0)	8 (28.6)	<0.001
	III trimester	6 (6.7)	12 (42.9)	
	entire pregnancy	51 (57.3)	8 (28.6)	
Medication during pregnancy	yes	73 (43.5)	33 (31.4)	0.047
	no	95 (56.5)	72 (68.6)	
Period during which medication was taken in pregnancy	I/II trimester	25 (36.2)	10 (31.3)	0.001
	III trimester	10 (14.5)	15 (46.9)	
	entire pregnancy	33 (49.3)	7 (21.9)	
Smoking during pregnancy	yes	48 (27.3)	9 (8.5)	0.0001
	no	128 (72.7)	97 (91.5)	

There were no statistically significant differences between the ADHD group and the control group in variables such as: maternal diseases before conception, nausea and vomiting during pregnancy, too low or too high maternal weight during pregnancy, falls, maternal injury during pregnancy, amniotic fluid amount, spotting, bleeding during pregnancy, doctors' concerns about the possibility of miscarriage or premature labor due to unremitting staining, pregnancy-induced hypertension, maternal epilepsy during pregnancy, premature rupture of the amniotic sac, alcohol consumption during pregnancy, drug use and use of medication of unknown origin during pregnancy.

Factors associated with delivery

Statistically significant differences between ADHD and control groups were found in relation to variables such as: mother's age at delivery, the use of pain reducing substances during delivery, and problems with the child during delivery. In both assessed groups, the majority of mothers at the time of childbirth were in the 25–35 age group (55.5% of mothers in the ADHD group and 73.6% of mothers in the control group). In the ADHD group, over a third of women (37.5%) gave birth to a child before the age of 25 and 8.8% after 35 years of age. In turn, in the control group, mothers <25 years of age accounted for 20.8% of respondents, and mothers >35 years of age for 5.7%. Over half of mothers from the ADHD group (54.8%) and 71.6% from the control group gave birth without anesthesia. Perinatal anesthesia was used in 45.2% of mothers from the ADHD group and 28.4% of mothers from the control group ($p = 0.009$). Nearly one-fourth of mothers from the ADHD group (24.4%) reported that complications occurred at the time of delivery (not analyzed), as opposed to 9.8% in the case of the control group ($p = 0.003$). Detailed data are presented in Table 2.

Table 2. **Incidence of risk factors associated with delivery in the ADHD and control groups (variables for which statistically significant differences were demonstrated)**

Factor	Answers	ADHD group n (%)	Control group n (%)	p
Age of mother at delivery	<25 years	65 (37.5)	22 (20.8)	0.009
	25–35 years	101 (55.5)	78 (73.6)	
	>35 years	16 (8.8)	6 (5.7)	
Use of pain reducing substances during delivery	yes	66 (45.2)	27 (28.4)	0.009
	no	80 (54.8)	68 (71.6)	
Incidence of problems with the child during delivery	yes	43 (24.4)	10 (9.8)	0.003
	no	133 (75.6)	92 (90.2)	

There were no statistically significant differences between the ADHD group and the control group in terms of variables such as: single/multiple delivery, date of delivery, type of delivery, use of induction drugs, child position during delivery, changes

in amniotic fluid, problems with the placenta, bleeding during delivery and problems with the umbilical cord being wrapped around the child's neck.

Factors associated with the condition of the child after birth

Statistically significant differences between the ADHD group and the control group were found for variables such as the APGAR score, neonatal oxygen administration, placement in an incubator, neonatal jaundice and its treatment, especially with the use of replacement transfusion, the presence of physical anomalies or other congenital problems, and other problems in the neonatal period. In both assessed groups, newborns after delivery usually received high scores on the APGAR scale, in the range of 8–10 points. In the control group, a higher percentage of newborns had a very low score, i.e., 1–4 points (9.0% vs. 6.6% in the ADHD group). In turn, in the ADHD group, the percentage of children with a score in the range of 5–7 points was 12.1% compared to 3.8% in the control group ($p = 0.003$). In the ADHD group, the percentage of children who required oxygen administration after delivery was 15.5% compared to 6.6% in the control group ($p = 0.033$). Newborns from the ADHD group were placed in an incubator just after delivery significantly more often when compared to the control group (26.2% in the ADHD group vs. 5.7% in the control group; $p = 0.0001$).

Jaundice was observed in 66.1% of newborns in the ADHD group and in 50.0% of newborns in the control group ($p = 0.008$). Newborns from the ADHD group were treated for jaundice significantly more often than the newborns in the control group (52.7% in the ADHD group vs. 21.0% in the control group; $p = 0.0001$). In 21.7% of children from the ADHD group, jaundice was treated with replacement transfusion (vs. 0.0% in the control group) and in 73.9% phototherapy was used (vs. 86.4% in the control group). Among the newborns in the ADHD group doctors determined physical abnormalities or congenital problems significantly more often (21.5% in the ADHD group vs. 8.5% in the control group; $p = 0.005$). The mothers in the ADHD group declared significantly more frequent incidences of problems with the child in the neonatal period (types of problems were not analyzed) (42.9% in the ADHD group vs. 8.6% in the control group; $p = 0.0001$). Detailed data are presented in Table 3.

Table 3. Incidence of risk factors associated with the condition of the child after birth in the ADHD and control groups (variables for which statistically significant differences were demonstrated)

Factor	Answer	ADHD group n (%)	Control group n (%)	p
APGAR score	1–4	12 (6.6)	1 (9.0)	0.003
	5–7	22 (12.1)	4 (3.8)	
	8–10	148 (81.3)	101 (95.3)	
Neonatal oxygen administration	yes	20 (15.5)	7 (6.6)	0.033
	no	109 (84.5)	99 (93.4)	

table continued on the next page

Placement in an incubator	yes	44 (26.2)	6 (5.7)	0.0001
	no	124 (73.8)	100 (94.3)	
Neonatal jaundice	yes	111 (66.1)	53 (50.0)	0.008
	no	57 (33.9)	53 (50.0)	
Neonatal jaundice treatment	yes	48 (52.7)	22 (21.0)	0.0001
	no	43 (47.3)	83 (79.0)	
Jaundice treatment method	phototherapy	17 (73.9)	19 (86.4)	0.048
	replacement	5 (21.7)	0 (0.0)	
	transfusion	1 (4.3)	3 (13.6)	
	other			
Physical anomalies or other congenital problems	yes	38 (21.5)	9 (8.5)	0.005
	no	139 (78.5)	97 (91.5)	
Problems in the neonatal period	yes	75 (42.9)	9 (8.6)	0.0001
	no	100 (57.1)	96 (91.4)	

No statistically significant differences were determined between the ADHD and control groups in relation to the child's birth weight.

Discussion

The Pregnancy and perinatal history questionnaire used in the study is a modification of the questionnaire by Buka et al. [25] (originally used to assess the number of obstetric complications and the reliability of foetal-perinatal history in patients diagnosed with schizophrenia). 90% of the ADHD group were boys, which reflects the typical sex distribution in studies with children diagnosed with attention deficit hyperactivity disorder [26]. Patients with the combined type ADHD were most numerous, which is consistent with reports of clinically treated populations (combined type ADHD constitutes approximately 60% of all diagnoses [27]). There were no statistically significant differences in the results obtained for subgroups identified by gender, hence further analyses and comparisons were made for entire groups without gender divisions (i.e., ADHD group and control group). Therefore, it can be assumed that differences in gender distribution in the ADHD and control groups do not affect the final results.

Risk factors associated with the course of pregnancy and delivery

Statistically significant differences between the assessed groups concerned the incidence of maternal diseases and other problems in the I/II trimester, mother's exposure to stress throughout the pregnancy and medication intake, as well as cigarette smoking during pregnancy, the mother's age at delivery being <25 years of age or >35 years of age, use of pain reducing substances during delivery and problems with the child during delivery.

The incidence of diseases during pregnancy affected more than a third of mothers from the ADHD group. Most of them were upper respiratory tract infections with temperatures not exceeding 38°C. More than half of these infections took place at the beginning of pregnancy – in the I/II trimesters, and in almost a third of the women (30.9%) this concerned the entire pregnancy period. A literature review yields reports confirming that exposure of the mother during pregnancy to various infections, especially viral infections, may be a risk factor for the development of ADHD. Viruses, which potentially increase the risk of ADHD, include the rubella virus, chickenpox, measles, influenza, or enterovirus 71 [28]. In addition, the importance of streptococcal infections is emphasized [29]. Other pathogens that may have a negative impact on the developing central nervous system (CNS) of the fetus and the emergence of symptoms of attention deficit hyperactivity disorder are cytomegalovirus and HIV [30]. This study did not analyze which pathogens were the cause of maternal infections during pregnancy, but it cannot be ruled out that at least some of them were caused by those listed above. Significantly more frequent incidence of other problems during pregnancy in the ADHD group (not mentioned in the questionnaire, including cervical insufficiency), as well as problems with the child during delivery, may pose a potential threat to the correct development of the fetal CNS.

In the case of exposure to stress/presence of emotional problems, most mothers stated that those were caused mainly due to situations related to everyday problems, including socio-economic conditions and family relations (conflicts, divorce, experience of violence). More than half of ADHD mothers reported that exposure to stress affected the entire pregnancy period, and over a third experienced excessive stress in the I/II trimester. The results of available studies indicate that exposure to stress during pregnancy, and especially in the first two of its trimesters, may have important implications in the etiology of ADHD. Research conducted by scientists from the University of Ottawa shows that children of women who have experienced excessive stress during pregnancy are twice as likely to suffer from behavioral disorders and attention deficit hyperactivity disorder [31]. In addition, studies by Rodriguez and Bohlin [32] have shown that the experience of stress during pregnancy influences the subsequent development of fully symptomatic ADHD, especially in boys. In turn, Grizenko et al. [13] showed that the stress experienced by pregnant mothers is not related to the intellectual level of children diagnosed with ADHD but is significant in relation to the severity of symptoms. However, experiments conducted on animal models prove that exposure to stress during pregnancy may affect structural changes in the CNS of the offspring, and may be associated with impaired attention and functioning of the dopaminergic system [33].

Almost half of the women in the ADHD group took medicines during pregnancy for various reasons, including nearly 50% throughout pregnancy, and over a third in the I/II trimesters of pregnancy. No analyses of the types of used medications were conducted. It is well known that the use of medicines in pregnancy always carries a risk of affecting the fetus – this factor is responsible for about 3% of developmental

congenital abnormalities in newborns. Additionally, side effects of medicine use appear at a later age in approximately 10% of children. There are reports on the use of antidepressants during pregnancy and the risk of ADHD in children [34]. The necessity of such treatment results from the incidence of anxiety or affective disorders in the pregnant woman, often caused by stressors. In the context of significantly more frequent exposure to excessive stress during pregnancy in mothers from the ADHD group, this is an important observation, although the study did not analyze whether mothers exposed to stress were treated pharmacologically.

Cigarette smoking during pregnancy was confirmed by almost a third of women from the ADHD group, and of those over 70% smoked throughout the entire pregnancy. Numerous reports confirm that the toxic components of tobacco smoke are the most common cause of low birth weight. Smoking is also associated with a higher incidence of spontaneous miscarriage, premature delivery, ectopic pregnancy, premature rupture of the amniotic sac, premature detachment of the placenta, as well as higher perinatal mortality of fetuses and newborns. It is also likely to affect the incidence of emotional and neurological disorders, also it significantly increases the risk of attention deficit hyperactivity disorder [35].

The relationship between smoking while pregnant and ADHD could be multifactorial. Firstly, pregnant women diagnosed with attention deficit hyperactivity disorder are more likely to smoke; secondly, smoking during pregnancy is common in mothers with hyperactive children; thirdly, smoking during pregnancy increases the risk of ADHD. Some researchers point out that prenatal exposure to tobacco smoke, as well as alcohol, may be associated with hyperactivity in children, but it is not a sufficient and independent etiological factor. Nevertheless, a study by Schwenke et al. [36] showed that children of smoking mothers often got lower APGAR scores in the first minute of their lives, compared to children of mothers who did not smoke, and that prenatal exposure to tobacco smoke in the first trimester of pregnancy had a significant association with ADHD.

In turn, research on the risk of attention deficit hyperactivity disorder in the offspring of mothers who were exposed to tobacco smoke during pregnancy (passive smoking) does not allow the formulation of final conclusions [9]. Therefore, the question of the extent to which genetic and environmental factors determine the presence of ADHD remains relevant. However, it can be assumed that in the case of mothers with ADHD who smoke during pregnancy, negative genetic and environmental determinants accumulate, in conjunction with the impact of environmental factors on gene expression.

In both assessed groups, most mothers were between 25 and 35 years of age during delivery, but in the ADHD group significantly more women gave birth before the age of 25 or after the age of 35. Along with the mother's increasing age, the reproductive potential is reduced, and the risk of fetal malformations, premature births and miscarriages increases. In turn, a younger age, especially below 18, frequently carries a risk of hypertension and intrauterine growth restriction. Studies carried out by Valdimars-

dóttir et al. [14] have shown that a mother's young age significantly increases the risk of ADHD in a child.

Nearly half of mothers from the ADHD group, significantly more than in the control group, used perinatal anesthesia. Administering pain reducing drugs too late during delivery may lead to suppression of the newborn's respiratory center. However, there are no detailed studies showing the relationship between administering drugs to reduce labor pain and the incidence of attention deficit hyperactivity disorder in children, hence it is difficult to unequivocally address the obtained results.

Factors related to the condition of the child after birth

In the ADHD group, there was a significantly higher percentage of newborns with an APGAR score in the range of 5–7 points. Published research proves the relationship between the APGAR score and the prognosis for the newborn – children who got a score in the range of 0–4 points in the first and fifth minute after birth are three times more likely to develop various neurological complications. Grizenko et al. [37] showed that children with ADHD who received a low score in the first minute of their lives presented more severe symptoms of attention deficit hyperactivity disorder. Suckdorff et al. [17] pointed to a similar relationship in their study. Similarly, Zappitelli et al. [18] claim that a score of <5 points presents a greater risk of ADHD. However, Schvenke et al. [36] state that a score of <7 points and cigarette smoking by pregnant mothers are associated with a significantly greater risk of developing ADHD. In this study, there were 12 (6.6%) children with ADHD with a low APGAR score, and 22 (12.1%) children with ADHD with a score lower than or equal to 7 points, which may indirectly indicate a significantly more frequent incidence of perinatal hypoxia in the ADHD group.

More than half of the ADHD children had neonatal jaundice, significantly more than in the control group. Importantly, more than half of them required treatment, again significantly more than in the control group. Over a fifth of children from the ADHD group were treated using replacement transfusion. These results are extremely important in the context of data demonstrating that an excessive increase in bilirubin can damage basal ganglia and lead to symptoms of bilirubin encephalopathy. These complications may occur with differing severity, with various consequences: starting from cognitive function disorders, including abstract thinking and attention disorders, to the most severe forms of cerebral palsy. A study by Wusthoff et al. [20] showed that significant hyperbilirubinemia increases the risk of neurodevelopmental disorders, including ADHD. A similar relationship between the incidence of hyperbilirubinemia and ADHD is indicated by Wei et al. [21]. Moreover, further significant intergroup differences, such as neonatal oxygen administration, placement in an incubator, physical anomalies or other problems in the neonatal period, may indicate a greater severity of problems in the adaptation period in the group of children with ADHD and constitute a risk of developing the disorder.

Research limitations

Several limitations affect the ability to infer from the obtained results. The relatively low sample size makes it impossible to conduct a detailed analysis of the frequency of individual risk factors. The study was conducted in groups of people with ADHD under psychiatric care, primarily among boys with combined type ADHD, which does not allow for generalization of the results. There was no psychiatric examination of children and adolescents qualified for the control group, hence it cannot be ruled out that people with ADHD were included. Some questions in the pregnancy and perinatal history questionnaire should be more precise (indications and groups of medications taken by mothers during pregnancy; analysis of the type of diseases and their causes in pregnant mothers; reasons for preterm delivery; indications for delivery by caesarean section or using delivery tools; analysis for mother's age at delivery <18 years of age). There was also no analysis of the presence of attention deficit hyperactivity disorder in mothers in the ADHD group.

Limitation of studies conducted using questionnaires are the lack of standardization, a large variance of errors and low reliability, which are influenced by mechanisms that restrict access to information (e.g., fear of judgement when admitting to consuming psychoactive substances). Moreover, the disadvantage of research in the *ex post facto* model is the inability to manipulate independent variables that have already influenced the tested variable (the possibility of only observing the effects of these interactions).

Conclusions

Significantly more frequent incidence of factors related to the course of pregnancy, delivery and the child's condition after birth, in the ADHD group when compared to the control group, such as: incidence of diseases and other problems in mothers in the I/II trimester, exposure to stress throughout the entire pregnancy and medication intake, smoking during pregnancy, the age of the mother at delivery being <25 years or >35 years, the use of pain reducing substances during delivery and the incidence of problems with the child during delivery, an APGAR score in the range of 5–7 points, neonatal jaundice requiring treatment, especially using replacement transfusion, physical anomalies/congenital problems, as well as adaptation problems requiring oxygen administration or placement in an incubator, may indicate the potential role of these factors in the etiology of psychomotor hyperactivity disorder.

References

1. Barkley RA, Fischer M, Smallish L, Fletcher K. *The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder*. J. Abnorm. Psychol. 2002; 111(2): 279–289.
2. Słopeń A. *Badania asocjacyjne genów kandydujących w zespole nadpobudliwości psychoruchowej i deficytu uwagi (ADHD) z wybranymi funkcjami poznawczymi*. Poznan: Science Publishing House of Poznan University of Medical Sciences; 2011.
3. Ben Amor L, Grizenko N, Schwartz G, Lageix P, Baron C, Ter-Stepanian M et al. *Perinatal complications in children with attention-deficit hyperactivity disorder and their unaffected siblings*. J. Psychiatry Neurosci. 2005; 30(2): 120–126.
4. Grizenko N, Qi Zhang DD, Polotskaia A, Joober R. *Efficacy of methylphenidate in ADHD children across the normal and the gifted intellectual spectrum*. J. Can. Acad. Child Adolesc. Psychiatry. 2012; 21(4): 282–288.
5. Grizenko N, Shayan YR, Polotskaia A, Ter-Stepanian M, Joober R. *Relation of maternal stress during pregnancy to symptom severity and response to treatment in children with ADHD*. J. Psychiatry Neurosci. 2008; 33(1): 10–16.
6. He Y, Chen J, Zhu LH, Hua LL, Ke FF. *Maternal smoking during pregnancy and ADHD: Results from a systematic review and meta-analysis of prospective cohort studies*. J. Atten. Disord. 2020; 24(12): 1637–1647. Doi: 10.1177/1087054717696766 (First Published March 8, 2017).
7. Sagiv SK, Epstein JN, Bellinger DC, Korrick SA. *Pre – and postnatal risk factors for ADHD in a nonclinical pediatric population*. J. Atten. Disord. 2013; 17(1): 47–57.
8. Thakur GA, Sengupta SM, Grizenko N, Schmitz N, Pagé V, Joober R. *Maternal smoking during pregnancy and ADHD: A comprehensive clinical and neurocognitive characterization*. Nicotine Tob. Res. 2013; 15(1): 149–157.
9. Dong T, Hu W, Zhou X, Lin H, Lan L, Hang B et al. *Prenatal exposure to maternal smoking during pregnancy and attention-deficit/hyperactivity disorder in offspring: A meta-analysis*. Reprod. Toxicol. 2018; 76: 63–70. Doi: 10.1016/j.reprotox.2017.12.010.
10. Mulligan RC, Knopik VS, Sweet LH, Fischer M, Seidenberg M, Rao SM. *Neural correlates of inhibitory control in adult attention deficit/hyperactivity disorder: Evidence from the Milwaukee longitudinal sample*. Psychiatry Res. 2011; 194(2): 119–129.
11. Pagnin D, Zamboni Grecco ML, Furtado EF. *Prenatal alcohol use as a risk for attention deficit/hyperactivity disorder*. Eur. Arch. Psychiatry Clin. Neurosci. 2019; 269(6): 681–687. Doi: 10.1007/s00406-018-0946-7.
12. Knopik VS, Heath AC, Jacob T, Slutske WS, Bucholz KK, Madden PA et al. *Maternal alcohol use disorder and offspring ADHD: Disentangling genetic and environmental effects using a children-of-twins design*. Psychol. Med. 2006; 36(10): 1461–1471.
13. Grizenko N, Fortier MÈ, Gaudreau-Simard M, Jolicoeur C, Joober R. *The effect of maternal stress during pregnancy on IQ and ADHD symptomatology*. J. Can. Acad. Child Adolesc. Psych. 2015; 24(2): 92–99.
14. Valdimarsdóttir M, Hrafnisdóttir AH, Magnússon P, Gudmundsson OO. *The frequency of some factors in pregnancy and delivery for Icelandic children with ADHD*. Laeknabladid. 2006; 92(9): 609–614.
15. Serati M, Barkin JL, Orsenigo G, Altamura AC, Buoli M. *Research review: The role of obstetric and neonatal complications in childhood attention deficit and hyperactivity disorder – A systematic review*. J. Child Psychol. Psychiatry. 2017; 58(12): 1290–1300.

16. Fitzgerald E, Boardman JP, Drake AJ. *Preterm birth and the risk of neurodevelopmental disorders – Is there a role for epigenetic dysregulation?* Curr. Genomics. 2018; 19(7): 507–521.
17. Sucksdorff M, Lehtonen L, Chudal R, Suominen A, Gissler M, Sourander A. *Lower Apgar scores and Caesarean sections are related to attention-deficit/hyperactivity disorder.* Acta Paediatr. 2018; 107(10): 1750–1758.
18. Zappitelli M, Pinto T, Grizenko N. *Pre-, peri-, and postnatal trauma in subjects with attention-deficit hyperactivity disorder.* Can. J. Psychiatry. 2001; 46(6): 542–548.
19. Hanć T, Szwed A, Słopeń A, Wolańczyk T, Dmitrzak-Węglarz M, Ratajczak J. *Perinatal risk factors and ADHD in children and adolescents: A hierarchical structure of disorder predictors.* J. Atten. Disord. 2018; 22(9): 855–863.
20. Wusthoff CJ, Loe IM. *Impact of bilirubin-induced neurologic dysfunction on neurodevelopmental outcomes.* Semin. Fetal. Neonatal. Med. 2015; 20(1): 52–57.
21. Wei CC, Chang CH, Lin CL, Chang SN, Li TC, Kao CH. *Neonatal jaundice and increased risk of attention-deficit hyperactivity disorder: A population-based cohort study.* J. Child Psychol. Psychiatry. 2015; 56(4): 460–467.
22. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (4th ed. rev.)*. Washington, DC: American Psychiatric Association; 2000.
23. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders, Diagnostic Criteria for research.* Geneva: WHO; 1993.
24. Wolańczyk T, Kołakowski A. *Kwestionariusze do diagnozy ADHD i zaburzeń zachowania (The diagnostic structured interview for ADHD and conduct disorder)*. Warsaw: Janssen-Cilag; 2005.
25. Buka SL, Goldstein JM, Seidman LJ, Tsuang MT. *Maternal recall of pregnancy history: Accuracy and bias in schizophrenia research.* Schizophr. Bull. 2000; 26(2): 335–350.
26. Skoggl EW, Teicher MH, Andersen PN, Hovik KT, Øie M. *ADHD in girls and boys-gender differences in co-existing symptoms and executive function measure.* BMC Psychiatry. 2013; 13: Article number 298. Doi: 10.1186/1471-244X-13-298.
27. Willens TE, Biederman J, Faraone V, Martelon M, Westerberg D, Spencer TJ. *Presenting ADHD symptoms, subtypes, and comorbid disorders in clinically referred adults with ADHD.* J. Clin. Psychiatry. 2009; 70(11): 1557–1562.
28. Chang LY, Huang LM, Gau SSF, Wu YY, Hsia SH, Fan TY et al. *Neurodevelopment and cognition in children after enterovirus 71 infection.* N. Engl. J. Med. 2007; 356(12): 1226–1234.
29. Waldrep DA. *Two cases of ADHD following GABHS infection: A PANDAS subgroup?* J. Am. Acad. Child Adolesc. Psychiatry. 2002; 41(11): 1273–1274.
30. Nozyce ML, Lee SS, Wiznia A, Nachman S, Mofenson LM, Smith ME et al. *A behavioral and cognitive profile of clinically stable HIV-infected children.* Pediatrics. 2006; 117(3): 763–770.
31. MacKinnon N, Kingsbury M, Mahedy L, Evans J, Colman I. *The association between prenatal stress and externalizing symptoms in childhood: Evidence from the Avon longitudinal study of parents and children.* Biol. Psychiatry. 2018; 83(2): 100–108.
32. Rodriguez A, Bohlin G. *Are maternal smoking and stress during pregnancy related to ADHD symptoms in children?* J. Child Psychol. Psychiatry. 2005; 46(3): 246–254.
33. Coe CL, Lulbach GR, Schneider ML. *Prenatal disturbance alters the size of the corpus callosum in young monkeys.* Dev. Psychobiol. 2002; 41(2): 178–185.
34. Morales DR, Slattery J, Evans S, Kurz X. *Antidepressant use during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder: Systematic review of*

- observational studies and methodological considerations*. BMC Med. 2018; 16(1): 6. Doi: 10.1186/s12916-017-0993-3.
35. Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP. *Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children*. Environ. Health Perspect. 2006; 114(12): 1904–1909.
 36. Schwenke E, Fasching PA, Faschingbauer F, Pretscher J, Kehl S, Peretz R et al. *Predicting attention deficit hyperactivity disorder using pregnancy and birth characteristics*. Arch. Gynecol. Obstet. 2018; 298(5): 888–895.
 37. Grizenko N, Eberle ML, Fortier ME, Côté-Corriveau G, Jolicoeur C, Joobor R. *Apgar scores are associated with attention-deficit/hyperactivity disorder symptom, severity*. Can. J. Psychiatry. 2016; 61(5): 283–290.

Address: Anita Bryńska
Medical University of Warsaw
Department of Child and Adolescent Psychiatry
02-091 Warszawa, Żwirki i Wigury Street 63a
e-mail: abrynska@wum.edu.pl